DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Randy Russell
Assistant Director, Regulatory Affairs
Alcon Research, Ltd.
6201 South Freeway, R3-54
Fort Worth, TX 76134-2099

RE: NDA 021861
PATANASE (olopatadine hydrochloride) Nasal Spray
MA #157

Dear Mr. Russell:

The Office of Prescription Drug Promotion (OPDP), Division of Professional Drug Promotion (DPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a professional sales aid (PTN12500SA) (sales aid) for PATANASE (olopatadine hydrochloride) Nasal Spray (Patanase) submitted by Alcon Research, Ltd. (Alcon) under cover of Form FDA-2253. The sales aid was also obtained at the American Academy of Nurse Practitioners National Conference held in Orlando, Florida, on June 20-24, 2012. The sales aid is false or misleading because it overstates the efficacy of Patanase. Thus, the sales aid misbrands Patanase in violation of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), 21 U.S.C. 352(a). *Cf.* 21 CFR 202.1(e)(6)(i) & (e)(7)(iii).

Background

Below is the indication and summary of the most serious and most common risks associated with the use of Patanase.[1] According to its FDA-approved product labeling (PI):

> PATANASE Nasal Spray is an H_1 receptor antagonist indicated for the relief of the symptoms of seasonal allergic rhinitis in adults and children 6 years of age and older.

The PI for Patanase contains Warnings and Precautions regarding local nasal effects including epistaxis, nasal ulceration, nasal septal perforation, and the need for caution when engaging in activities requiring complete mental alertness. In addition, according to the Adverse Reactions section of the PI, the most commonly reported adverse reactions associated with the use of Patanase include bitter taste, headache, epistaxis, pharyngolaryngeal pain, post-nasal drip, cough, urinary tract infection, CPK elevation, dry mouth, fatigue, influenza, nasopharyngitis, somnolence, and throat irritation in patients 12 years of age and older. In patients 6 to 11 years of age the most commonly reported adverse reactions were epistaxis, headache, upper respiratory tract infection, bitter taste,

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

pyrexia, and rash.

Overstatement of Efficacy

Promotional materials are misleading if they suggest that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience. The sales aid includes the following claims and presentations (emphasis in original):

- "**Congestion relief in 30 minutes**"
- "**Patanase® Nasal Spray is the only nasal antihistamine FDA approved to relieve symptoms in 30 minutes.**[2]"
- A series of checked boxes representing the symptoms of "**congestion**, sneezing, runny nose, itchy nose," and "TNSS[2,3,4,5]" with "congestion" presented in bold red font
- Graphics of a woman and child with a cork in each nostril on the front of the sales aid and the contrasting image of the same woman and child without corks in their nostrils on the back of the sales aid.
- The tagline "**Unplug with**" in conjunction with a graphic of two loose corks and the Patanase logo

The totality of this presentation is misleading because it implies that Patanase has been shown to be effective in the treatment of the specific symptom of nasal congestion, when this has not been demonstrated by substantial evidence or substantial clinical experience. The clinical studies used for approval of Patanase evaluated a composite measure of symptoms and did not specifically evaluate efficacy for the individual symptom of nasal congestion. According to the Clinical Studies section of the PI, the assessment of efficacy for the treatment of the symptoms of seasonal allergic rhinitis was based on the **total** nasal symptom score (TNSS), where TNSS was calculated as the sum of the patient or caregiver's scoring of the four individual symptoms of nasal congestion, rhinorrhea, itchy nose, and sneezing. Demonstrating an effect on the composite total nasal symptom score does not represent a clear effect on any individual component of the TNSS. In addition, the three studies[3,4,5] cited as references in the sales aid were conducted in allergen chamber environmental exposure units (EEU). These EEU studies were pharmacodynamic studies conducted in controlled settings that do not reflect real world situations. Therefore, the clinical studies used for approval of Patanase and the cited references are not considered substantial evidence to support a claim of efficacy specifically for nasal congestion.

In addition, claims such as, "**Patanase® Nasal Spray is the only nasal antihistamine FDA approved to relieve symptoms in 30 minutes**," (emphasis in original) suggest a guarantee of clinical symptom relief within 30 minutes of administration of the drug. The PI, cited to support these claims and presentations, states, "In [the three 2-week seasonal

[2] PATANASE® Nasal Spray package insert.
[3] Patel D, Garadi R., Brubaker M, et al. Onset and duration of action of nasal sprays in seasonal allergic rhinitis patients, olopatadine hydrochloride versus mometasone furoate monohydrate. *Allergy Asthma Proc.* 2007;28(5):592-599.
[4] Patel P, Roland PS, Marple BF, et al. An assessment of the onset and duration of action of olopatadine nasal spray. *Otolaryngol Head Neck Surg.* 2007;137(6):918-924.
[5] Patel P, Patel D, Edwards M, et al. Onset of action of olopatadine hydrochloride nasal spray 0.6% (Patanase®) in the treatment of allergic rhinitis. Poster presented at: American Academy of Allergy, Asthma, & Immunology (AAAAI) 2008 Annual Meeting; March 14-18, 2008: Philadelphia, PA.

allergy trials] . . . onset of action was seen after 1 day of dosing . . . . In the [three environmental exposure unit studies] PATANASE Nasal Spray 0.6% was found to have an onset of action of 30 minutes after dosing in the environmental exposure unit." Presenting onset of action claims based on allergen chamber environmental exposure unit (EEU) studies alone misrepresents the onset of clinical symptom relief with Patanase. As reflected in the pivotal 2-week seasonal allergy clinical trials, patients receiving Patanase experienced an onset of action after one day of dosing.

The sales aid also includes the following claims and presentation (emphasis in original):

- "**Sustained symptom relief, week after week.**[6,7,8]"
- A graph depicting "% Change in TNSS from baseline" over time in conjunction with an embedded arrow labeled "Ongoing relief through Day 14" with the arrowhead starting and extending beyond the 14 day time point.

The totality of these claims and presentation misleadingly overstates the efficacy of Patanase by suggesting that symptom relief is maintained beyond 14 days. The studies[6,7,8] cited as references do not support the claim because they were not designed to measure efficacy beyond 14 days. We acknowledge that the claim "Sustained TNSS improvement through 2 weeks" appears within the graph. However, this does not mitigate the misleading impression created by the totality of this presentation. Furthermore, the graph presents the data from the studies as a pooled average. Such pooling may overestimate the statistical significance of any differences between the active and placebo treatment arms.

Conclusion and Requested Action

For the reasons discussed above, the sales aid misbrands Patanase in violation of the FD&C Act, 21 U.S.C. 352(a). *Cf.* 21 CFR 202.1(e)(6)(i) & (e)(7)(iii).

OPDP requests that Alcon immediately cease the dissemination of violative promotional materials for Patanase such as those described above. Please submit a written response to this letter on or before November 28, 2012, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Patanase that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Professional Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. Please note that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has been reorganized and elevated to the Office of Prescription Drug Promotion (OPDP). OPDP consists of the Immediate Office, the Division of Professional Drug Promotion (DPDP) and the Division of Consumer

[6] Ratner PH, Hampel FC, Amar NJ, et al. Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis to mountain cedar. *Ann Allergy Asthma Immunol.* 2005;95(5):474-479.
[7] Meltzer EO, Hampel FC, Ratner PH, et al. Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immnunol.* 2005;95(6):600-606.
[8] Data on file.

Drug Promotion (DCDP). To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. In addition, OPDP recently migrated to a different tracking system. Therefore, OPDP letters will now refer to MA numbers instead of MACMIS numbers. Please refer to MA # 157 in addition to the NDA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Patanase comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Roberta Szydlo, R.Ph.
Regulatory Review Officer
Division of Professional Drug Promotion
Office of Prescription Drug Promotion

{See appended electronic signature page}

Lisa Hubbard, R.Ph.
Group Leader
Division of Professional Drug Promotion
Office of Prescription Drug Promotion

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/s/

ROBERTA T SZYDLO
11/13/2012

LISA M HUBBARD
11/13/2012